## REMARKS

The Examiner provides ONLY rejections based on 35 U.S.C. 103(a). All other rejections appear to be withdrawn. Importantly, the Examiner has CHANGED the references and made different combinations.

As an overall response, Applicant must protest the introduction of these new references (Punt et al, Bidney et al., and Bishop et al.) in this prosecution at this late date - particularly since the claims were NOT amended in the prior response (only some dependent claims were added). The MPEP requires that rejections be made at one time - so as to avoid a constantly moving target.

Second, the Examiner has not (it would appear) carefully read these new references. Some of them provide systems that are very limited in scope with variable results. None of the new references suggest the application to the specific genes in the pending claims. Indeed, none of the new references even demonstrate - with other genes - the ability to co-express two enzymes in a pathway so as to make a final product. Thus, they do NOT provide EVIDENCE of a reasonable likelihood of success. These problems are discussed in detail with respect to each of these references.

### A. The Teachings of Punt et al. Add Nothing

The Examiner makes four (4) separate rejections based on 103(a) - but ALL of them rely on the Punt et al. reference. Specifically, Claims 1, 13, 15-22 and 39 are rejected for allegedly being obvious over Benning and **Punt** in view of Essignmann et al. Claims 23-25 are rejected as allegedly obvious over Benning and **Punt** in view of Essignmann et al. together with Bidney. Claims 1, 13, 15-16, 26-31 and 40 are rejected for allegedly being obvious over Benning and **Punt** in view of Essignmann et al. together with Bevan. Claims 23-25 are rejected as allegedly obvious over Benning and **Punt** in view of Essignmann et al. together with Bevan and Bidney. Since every rejection now pending relies on the Punt et al. reference, it is very important to CAREFULLY look at this reference (and not merely make assumptions based on a cursory review).

The Examiner argues that the Punt reference teaches "transformation and co-transformation of heterologous proteins in E. coli." (Office Action, p.3). THIS IS NOT CORRECT! The Punt reference (as noted in the title) describes transformation of *Aspergillus*

- a fungus - using a selection marker from *E. coli*. With all due respect, the Examiner's gross mischaracterization of the SCIENCE in the Punt et al. reference suggests the Examiner gave the reference only a cursory review.

When the Punt et al. reference is carefully reviewed, it is clear that the expression system is 1) limited to particular host cells, 2) variable in results, and 3) completely untested with respect to producing a product from two enzymes. With regard to the first point, the reference notes at the outset (p. 119) the limitations of the system:

> "A prerequisite for the use of HmB resistance as a selection marker in *Aspergillus* transformation is the sensitivity of host strains to this drug."

Thus, the system is only applicable to related fungi with this particular sensitivity. With regard to the second point, the results (p. 121) showed that the transformation produced variable results:

> "The observed differences in resistance might be due to differences in the number of copies of pAN7-1 in the transformants. However, since in all transfromants the vector DNA was integrated into the chromosomal DNA (see next paragraph) differences in resistance may also be due to differences in chromosomal environment of the integrated pAN7-1 sequences."

In other words, since the site of integration is not controlled, some sites will have a negative impact on expression.[1] Finally, at no point does Punt et al. demonstrate that the ability to co-express two enzymes in a pathway so as to make a final product - let alone the final product specifically required in the pending claims! Thus, there is no EVIDENCE provided by the Punt et al. reference[2] that goes to the question of whether there is a likelihood of success WITH THE PARTICULAR GENES SET FORTH IN THE CLAIM.

In view of these deficiencies, the record does NOT support even the *combination* of Punt et al. with the other references. WHY would one skilled in the art even consider the Punt et al. reference, given the limitations on the host cell (i.e. fungi with a particular drug sensitivity), given the variable results (which cannot be controlled since the site of integration is not controlled), and given THE COMPLETE LACK OF ANY DEMONSTRATION that two enzymes in a pathway could be co-expressed so as to make a final product?

---

[1] The Examiner is not free to simply ignore these negative features of the reference.

[2] The other two references used in the combination also provide no EVIDENCE in this regard.

There is no motivation - AT ALL - to use the system in Punt et al. in the manner the Examiner suggests. The Examiner points to NOTHING within the Punt et al. reference that suggests the combination. With all due respect, it would appear that the Examiner has simply grabbed it randomly from the literature without carefully reviewing the totality of the contents.

Importantly, now that the deficiencies are clear (from a careful reading), ALL of the 103 rejections are undermined. First, as noted, there is no basis for combining Punt et al. with any of the other references. Second, even if improperly combined, it adds nothing to the question of likelihood of success. Because ALL of the rejections are undermined, they must ALL be withdrawn on these arguments alone.

**B. The Bishop et al. Reference Adds Nothing**

While the Examiner does not use the Bishop et al. reference (the '962 patent) in a formal combination of references, the Examiner (at p. 3 of the Office Action) heavily relies on the Bishop et al. reference for an alleged general teaching:

> "It is well known in the art that expression systems that produce several gene products simultaneously are very useful in synthesis of products involving consecutive enzymatic processes."

THIS IS NOT CORRECT! In fact, the Bishop et al. reference describes the making of products involving consecutive enzymatic processes as one of "the more challenging aspects of molecular biology." ('962 patent, Col. 1, lines 24-25). The Examiner MUST read Bishop et al. in context. He says that it is one of the more "challenging" problems in the whole field of molecular biology! This does not translate into "it is well known in the art" or "very useful." The Examiner appears to be suggesting that the problem is solved. And yet, looking at EACH experiment set forth in the Bishop et al. reference, one does not find even a SINGLE experiment demonstrating that two enzymes in a pathway could be co-expressed so as to make a final product.

The Bishop et al. reference is specific to vectors for transfecting insects using the baculovirus system. The examples do not involve co-expression of two enzymes in a pathway to synthesize a product. Thus, this reference does not provide EVIDENCE in support of the likelihood of success question. Absent EVIDENCE, the problem remains "challenging."

**C. The Bidney Reference Adds Nothing**

The Examiner argues that the Bidney reference provides a system that "offers the potential to regenerate transgenic cells at relatively high frequencies . . ." (Office Action, p. 7). Whether it "offers the potential" or not, there is not a SINGLE example among the seven (7) examples in the specification that involves co-expression of two enzymes in a pathway to synthesize a product. Once again, there is no EVIDENCE - even with other genes - that this will work - let alone the question of whether it would work for the two SPECIFIC genes in the pending claims.

**D. The Examiner Admits The Other References Are Deficient**

Applicants again point out that the Examiner has admitted to the deficiencies of the other cited references, as follows:

1. The Examiner admits that the primary reference, Benning, "does not teach a method of producing UDP-SQ from UDP-glucose with the polypeptide encoded by SEQ ID NO:6." (previous Office Action, p. 3).

2. The Examiner points to nothing in Benning about the expression of *both* genes in a host cell.

3. Essigmann is cited merely for the SQD1 gene; again, the Examiner points to nothing in about the expression of *both* genes in a host cell.

4. The Examiner admits that Essigmann teaches that the sulfur donor is unknown; the Examiner apparently (incorrectly) considers it sufficient under patent law that "sulfite is a *plausible* sulfur donor."

5. The Examiner cites to catalogs (Stratagene) merely for "vectors and host cells *capable* of undergoing multiple transformations." (Office Action, p. 4, emphasis added).

6. The Examiner argues there is motivation to combine because of "*possibly* to increase the efficiency . . ." (this Office Action, p. 4, emphasis added)

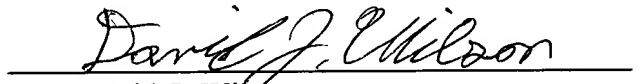
Applicants submit that the above arguments collectively demonstrate that the Examiner a) is personally providing an argument of "desirability" and b) has established nothing other than the introduction of both genes into a single host cell might be - in light of the present specification - something to "try." With respect to the element of desirability, it is not for the Examiner to provide this element. The Federal Circuit has noted that: "The mere fact that the

prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). With respect to the Examiner's arguments about what is "possible," the Federal Circuit has made it clear that the argument that something is "obvious to try" is a discredited and impermissible standard. *American Hospital Supply Corp. v. Travenol Laboratories, Inc.*, 745 F.2d 1, 223 USPQ 577 (Fed. Cir. 1984) ("Of course, an 'obvious to try' standard is not a legitimate test of patentability.") As a result, the rejections are not supportable.

## CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.984.0616.

Dated: December 1, 2003



David J. Wilson
Registration No. 45,225

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
617-984-0616